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Review Article

Melatonin therapy for REM sleep behavior disorder: a critical review of evidence

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ABSTRACT

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia associated with dream enactment often involving violent or potentially injurious behaviors during REM sleep that is strongly associated with synucleinopathy neurodegeneration. Clonazepam has long been suggested as the first-line treatment option for RBD. However, evidence supporting melatonin therapy is expanding. Melatonin appears to be beneficial for the management of RBD with reductions in clinical behavioral outcomes and decrease in muscle tonicity during REM sleep. Melatonin also has a favorable safety and tolerability profile over clonazepam with limited potential for drug–drug interactions, an important consideration especially in elderly individuals with RBD receiving polypharmacy. Prospective clinical trials are necessary to establish the evidence basis for melatonin and clonazepam as RBD therapies.

1. Introduction

Parasomnias are undesirable phenomena that occur during or around sleep. Without appropriate diagnosis, patients may undergo extensive medical workup and exposure to unnecessary pharmacotherapy [1]. Parasomnias are characterized according to the stage of sleep in which they occur (ie, rapid eye movement or REM or non-rapid eye movement or NREM sleep). NREM parasomnias including night terrors, somnambulism, and confusional arousals are most prevalent in pediatric populations. By contrast, in REM sleep behavior disorder (RBD), an REM parasomnia, the usual age of onset is between 40 and 70 years of age in adults and the elderly [2]. RBD is believed to be a result of brain-stem dysfunction, most likely involving the dorsal pontine sublateral dorsal nucleus and/or magnocellular reticular formation (± their afferent and efferent connections), leading to loss of the brain's normal ability to regulate physiologic REM sleep atonia [2,3]. The absence of appropriate central nervous system regulation of REM sleep atonia then may result in dream enactment, leading to complex motor behaviors paralleling dream content including talking, arm flailing, punching, kicking, or other potentially violent behaviors [4]. Behaviors exhibited in RBD may place both the patient and the bed partner at the risk of physical harm, with between 32% and 64% injuring either themselves or their bed partner, respectively [5,6]. In one case series of 96 patients, the incidence of bone fracture during RBD was found to be 7% [7]. More severe cases involving strangulation and subdural hematoma have also been reported [5,6,8–10]. The majority of RBD cases occurring in older adults remain idiopathic, at least initially, although a presumptive underlying cause of synucleinopathy neurodegeneration and eventual emergence of overt parkinsonism, or autonomic or cognitive dysfunction has been recognized in recent years [2,11–16], and RBD may also be seen in younger adults associated with narcolepsy and antidepressant use [17,18]. Several other medications have also been associated with either the emergence or worsening of RBD (see Table 1) [19]. Clonazepam, a benzodiazepine, is a pharmacologic agent that has been the most commonly used treatment for RBD [7,20,21]. The beneficial effects of melatonin in RBD were first described in 1997 by Kunz and Bes [22]. Subsequently, further literature and guidelines have suggested melatonin to provide clinical benefits in patients who require pharmacologic treatment for RBD [2,20,21,23]. The following is a review of the literature evaluating melatonin for the management of RBD.

2. Melatonin

Melatonin is a hormone that is secreted in a circadian rhythm from the pineal gland. Its secretion is influenced by dark

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Table 1
Medications associated with occurrence or worsening of RBD [19].

Caused by acute administration	Caused by withdrawal
Selective serotonin reuptake inhibitors	Ethanol
Selective serotonin/norepinephrine reuptake inhibitors	Benzodiazepines
Tricyclic antidepressants	Barbiturates
Monoamine oxidase inhibitors	Meprobamate
Mirtazapine	Pentazocine
Cholinesterase inhibitors	
Beta-blockers	
Tramadol	
Caffeine	

environments with melatonin serum levels beginning to rise shortly after nightfall and peaking during the middle of the night (ie, approximately 2–4 AM) [24]. The secretion may be reduced as a result of environmental light, severe illness, pineal calcification, or advanced age [25–28]. While low doses of melatonin have been evaluated, doses of 2–6 mg are generally necessary for clinical effect. An exogenous dose of 1 and 10 mg of melatonin can, respectively, increase serum melatonin concentrations 10 to 100 times the physiologic concentrations after 1 h of administration, with concentrations declining to baseline roughly 4–8 h post ingestion [29].

3. Literature search

A search was performed of MEDLINE and PubMed databases for studies between 1966 and February 2014, using the search terms "melatonin" and "REM sleep behavior disorder." The search was limited to studies on adult populations written in English language. The studies included prospective randomized controlled trials, clinical trials, prospective open-label trials, prospective comparative studies, and retrospective case series. The Cochrane Database of Systematic Reviews and reference lists of included trials were also searched to identify any additional relevant publications. A total of 39 abstracts were identified initially and were reviewed independently by two authors (IM and JL) who judged their appropriateness for inclusion. Articles that met the inclusion criteria were read in their entirety. A third author (ES) assisted with the selection of additional relevant studies. Four prospective and two retrospective reports of melatonin for the treatment of RBD were identified and can be found in Table 2. No articles were found in the Cochrane Database of Systematic Reviews, nor were there any additional trials identified from a review of the included article references.

4. Prospective trials evaluating melatonin use in RBD

A randomized, double-blind, placebo-controlled crossover trial evaluated the effects of melatonin on the percentage of REM sleep without atonia (RSWA) and clinical global improvement scores in subjects with RBD. A total of eight male subjects, mean age of 54 years, diagnosed with RBD per the International Classification for Sleep Disorder (ICSD) and reported RBD symptoms for 5–20 years were included in this trial. Several subjects had concomitant disorders including narcolepsy with periodic limb movement disorder ($n = 2$), Parkinson's disease ($n = 1$), and idiopathic insomnia ($n = 2$). Subjects were excluded if they had performed shift work within the last year, poor sleep hygiene, a Diagnostic and Statistical Manual of Mental Disorders 4th ed. (DSM-IV) psychiatric diagnosis, pathological brain imaging findings, changes of any medication within the past month, or ingestion of any medication that may interfere with melatonin levels or REM sleep. The subject with Parkinson's disease was noted to only receive one medication (375 mg/d L-dopa) during this trial, whereas all other subjects were noted to be medication free during the study period. The subjects were randomized to receive either placebo or melatonin 3 mg nightly during the 4-week study. This was followed by a 3–5-day washout period and switching of treatment assignments. A polysomnography (PSG) recording was performed three times in all subjects: baseline and after the end of both treatment assignments. Clinician's global improvement (CGI) was assessed at baseline and at the end of each treatment

Table 2
Included Prospective and Retrospective Reports of Melatonin use in RBD [21,23,30–33].

Prospective Reports				
Author	*N*	Population	Treatment	Results
McCarter et al., 2013	45	• PSG-diagnosed RBD • Mean age 66 years • 77% male • Demographically diverse	• Open-label melatonin • Open-label clonazepam • Naturalistic survey	• Significant reductions in frequency and severity of dream enactment behavior in both melatonin and clonazepam groups ($p < 0.05$) • Statistically significant reduction of falls and injury found in melatonin ($p < 0.05$) was not found in clonazepam ($p > 0.05$)
Kunz and Mahlberg, 2010	8	• PSG-diagnosed RBD • Mean age 54 years • 100% male	• Melatonin 3 mg nightly or placebo • 4 weeks of treatment • Crossover design	• Melatonin significantly decreased REM sleep without atonia ($p = 0.012$) • Melatonin decreased CGI score 1.5 points compared to baseline ($p = 0.024$)
Takeuchi et al., 2001	15	• PSG-diagnosed RBD • Mean age 63.5 years 93% male	• Melatonin 3–9 mg nightly • Open-label dosing • Duration of treatment not disclosed	• Melatonin significantly decreased tonic REM sleep ($p < 0.01$) • Twelve subjects reported at least 50% reduction of RBD symptoms with melatonin use
Kunz and Bes, 1999	6	• PSG-diagnosed RBD • Mean age 54 years • 50% male	• Melatonin 3 mg nightly • 6 weeks of treatment	• Melatonin significantly decreased REM sleep without atonia ($p = 0.028$) • Five subjects reported improvement of RBD symptoms within 1 week of treatment
Retrospective Reports				
Author	*N*	Population	Treatment	Results
Lin et al., 2013	28	• PSG-diagnosed RBD • Mean age of 66.5 years • 72% male	• Retrospective review • Clinical protocol consisted of 6 mg melatonin nightly for 4 months, then addition of 0.5–1 mg clonazepam	• Significant reductions of nights with dream-acting-out, nights with vocalizations, and percent of high EMG during total REM sleep time from baseline with the use of melatonin alone and with combination therapy ($p < 0.05$)
Boeve et al., 2003	14	• 93% male • Various neurologic disorders	• Retrospective review • Open label melatonin (3–12 mg) nightly • Concomitant clonazepam (0.5–1 mg) nightly in seven patients	• Clinical symptom response was controlled in six patients, markedly improved in four patients, short-term benefit in two patients, and either not improved or clinically worse in two patients

period. The Wilcoxon signed-rank test was used to evaluate differences in sleep parameters between groups. At the conclusion of the study, the authors reported that melatonin decreased the percentage of RSWA from 39.2% to 26.8% ($p = 0.012$) and sleep-onset latency by 1.96 min ($p = 0.05$) compared to baseline; however, a statistically significant change was not found when compared to placebo. Melatonin produced a decrease in the percentage of REM epochs with >50% of epochs with muscle tone ($p = 0.012$) compared to baseline, a change that was not found with placebo. Placebo administration after the crossover period showed a decrease in sleep-onset latency from baseline (–2.03 min, $p = 0.043$), but this change was not found in the melatonin group. No other sleep variables measured (sleep-onset latency, REM-onset latency, total sleep time, sleep period time, wake after sleep onset or WASO, sleep efficiency, REM density, phasic muscle twitches, and percent sleep in N1, N2, N3, and REM sleep) demonstrated a statistically significant change. A decrease in CGI score severity averaged 1.5 points ($p = 0.024$) and 0.5 ($p = 0.102$) with melatonin and placebo administration, respectively, compared to baseline. CGI change compared between placebo and melatonin was statistically significant ($p = 0.031$). Seven of the eight subjects reported improvement in RBD symptoms [complete resolution ($n = 4$), marked improvement ($n = 2$), and little improvement ($n = 1$)]. Symptom improvements were reported within the first week of treatment and continued to improve over the 4-week study period. No subjects reported adverse events from melatonin treatment. The authors concluded that treatment with melatonin effectively improved the clinical and neurophysiological aspects of RBD, although the most effective dose and duration are yet to be determined. Authors also note that melatonin had continued effects after administration was stopped due to statistically significant decreased RSWA found in the placebo group after assignment crossover. Although the study was well designed, several limitations should be considered. In this small study, the use of additional medications was minimal, suggesting the study population was relatively healthy, which may limit the generalizability of the findings. Secondary outcomes are particularly difficult to interpret as type II errors could be likely, given the very small sample size and lack of an a priori known effect size on which to design an appropriately powered study. However, the results of this small pilot prospective trial showed that melatonin administration of 3 mg nightly produced a statistically significant decrease in RSWA as well as subjective improvements in the clinical symptoms of RBD [30].

An open-label trial assessed the effects of exogenous melatonin in six subjects with PSG-confirmed RBD over a 6-week period. The subjects included had concomitant disease of hypertension ($n = 2$), Parkinson's disease ($n = 1$), and sympathetic dysautonomia ($n = 1$). Brain imaging was reported as normal in all subjects. The subjects were not allowed to take medications that could interfere with REM sleep (benzodiazepines, antidepressants, beta-blockers, or anti-inflammatory drugs). Medications reported to be used during the study period included L-dopa ($n = 1$), nifedipine ($n = 2$), furosemide ($n = 1$), and fludrocortisone ($n = 1$). The subjects had a mean age of 54 years and were described to have RBD symptoms for an average of 13 years. RBD symptoms reported included: nightly screaming and yelling ($n = 6$), jumping/falling out of bed once weekly during frightening dreams ($n = 2$), jumping/falling out of bed three to five times weekly during frightening dreams ($n = 2$), chronic exhaustion ($n = 2$), and early retirement due to impaired functioning ($n = 2$). The subjects took melatonin 3 mg nightly prior to bedtime. The subjects had PSG recordings at baseline and after 6 weeks of therapy. All subjects had lack of atonia at baseline per PSG findings. Changes in PSG data were analyzed with the Wilcoxon matched-pairs signed-rank test. Motor activity during sleep was assessed with actigraphy for a 2-week period at baseline and during treatment weeks 5 and 6. After 1 week of treatment, five subjects reported an improvement in RBD symptoms and were considered to respond to therapy. None of the responding subjects fell or jumped out of bed during treatment, and yelling during sleep was reduced from every night to once weekly. Melatonin respondents reported a reduction in frightening dreams from baseline, as no frightening dreams were reported during the treatment period. The majority of PSG measurements did not change over the duration of treatment. The percentage of RSWA yielded a statistically significant decrease from 32% to 11% ($p = 0.028$). The movement time in REM (percent per minute) showed a statistically significant decrease from 4.36 to 1.2 ($p = 0.043$). The actigraphy data showed a slight reduction of movements per minute percent time in bed (30.5 at baseline to 28.6 post treatment), although these findings were not statistically significant ($p = 0.17$). Additionally, percent wake time after sleep onset trended toward improvement (21.6 at baseline to 11.6 post treatment) but was not statistically significant ($p = 0.29$). After discontinuation of melatonin, the RBD symptoms were reported to return in all responding subjects (range 1–22 months) [31]. The one subject who did not report improvement in RBD symptoms was non-adherent to melatonin administration times and had poor sleep hygiene [34]. The authors concluded that treatment with melatonin 3 mg improves the clinical symptoms of RBD and restores the circadian modulation of REM sleep in subjects with internal desynchrony. The small sample size and lack of placebo comparator are limitations of this study. As the method of evaluating clinical outcomes was not reported (ie, structured interview, questionnaire, etc.), the consistency of obtaining reports is unknown, which questions the internal validity of the study. The statistically significant objective reductions in percent RSWA and movement time during REM sleep occurred within the first week of treatment with reemergence of symptoms after melatonin discontinuation suggesting that melatonin 3 mg at bedtime provides benefit in the treatment of RBD [31].

An open-label trial evaluated the effects of exogenous melatonin in 15 adults with RBD confirmed by PSG and symptomatic history. The average age of all subjects was 63.5 years and all but one subject was male. The subjects were allowed to take 3, 6, or 9 mg of melatonin according to the degree of clinical RBD symptoms. When symptoms were determined to be improved and/or stable, a repeat PSG and melatonin serum concentration was conducted. The PSG findings showed that the percentage of tonic REM activity decreased from 16.43% to 5.99% after melatonin treatment ($p < 0.01$). While a trend toward increased total sleep time, increase in the number of REM periods each evening, and decrease in the percentage of phasic REM activity occurred, none of these differences were statistically significant. A subjective improvement in RBD symptoms occurred in 13 subjects. Potentially injurious symptoms or injuries (vigorous sleep behaviors, ecchymoses, lacerations, and fractures) were reported to be reduced by 25% ($n = 1$), 50% ($n = 9$), and 75% ($n = 3$). Few subjects complained of adverse effects from melatonin such as excess morning sedation or weakness. The authors concluded that melatonin therapy greatly improved the clinical symptoms of RBD, and that melatonin may be a useful alternative to clonazepam, especially in elderly patients as adverse events were minimal. Numerous limitations regarding study design lead to challenges with interpretation of data in this small study, including a lack of reporting therapy duration, the time to clinical improvement, concomitant disease states, and additional medications allowed. Important details not described include the dosage of melatonin and corresponding degrees of response, methodology of assessing clinical improvements, and the tracking of melatonin adherence. Adverse effects were not reported. While melatonin appeared to improve the clinical outcomes in RBD in this study, the inherent limitations and lack of reporting leave clinicians with little insight into effective dosing, duration of therapy needed for clinical improvement, and clinical improvement expectations upon dosage changes [32].

A naturalistic survey of patient-reported clinical outcomes in patients with RBD offers additional support for the use of melatonin in RBD. A total of 133 adult patients who had been diagnosed with RBD between 2008 and 2010 were sent a survey in order to assess outcomes between common therapies. A total of 45 patients responded and were eligible for inclusion; among these patients, 25 were initially taking melatonin, 18 were initially taking clonazepam, and two were taking both. The survey was completed by the patient and their bed partner or a family member who had witnessed their RBD. The survey used an analog scale that assessed baseline and posttreatment RBD behaviors including frequency, severity, behavior type, falls, and injury. The patients included were 78% male, averaged an age of 66 years old, and had mean RBD symptom onset at 54 years of age. The majority of patients had a comorbid neurodegenerative disorder (53%) or received a selective serotonin/norepinephrine reuptake inhibitor antidepressant (56%). Thirteen patients (29%) were diagnosed with depression and 30 patients (67%) were diagnosed with obstructive sleep apnea (OSA). Only three patients in each treatment group reported complete remission of RBD symptoms with no statistically significant difference found between groups ($p = 0.68$). Both treatments decreased the frequency and severity of dream enactment behavior [pre- vs. posttreatment melatonin, 6.6 vs. 4.2 ($p = 0.0001$); pre- vs. posttreatment clonazepam, 6.5 vs. 4.1 ($p = 0.0005$)], but no difference was found between treatment groups. A significant reduction in falls and injury was demonstrated with melatonin [pre- vs. posttreatment falls, 60% vs. 20% ($p = 0.002$); pre- vs. posttreatment injury, 64% vs. 20% ($p = 0.001$)]. These findings were not replicated with statistical significance (although trends were suggested) for the clonazepam group (pre- vs. posttreatment falls, 67% vs. 33% ($p = 0.07$); pre- vs. posttreatment injury, 61% vs. 33% ($p = 0.06$)). The reported effective doses of melatonin in patients were ≤6 (52%), 9–12 (32%), and 15–25 mg (16%). The reported effective doses of clonazepam in patients were ≤0.5 (56%), 1 (11%), 2 (22%), and 3 mg (6%). Patients taking clonazepam reported a higher percentage of all adverse effects versus melatonin, although these were not statistically significant [overall adverse event 61% vs. 33% ($p = 0.07$); unsteadiness 39% vs. 8% ($p = 0.07$); dizziness 22% vs. 4% ($p = 0.08$)]. The discontinuation of treatment rates was not statistically significant between groups [28% for melatonin and 22% for clonazepam ($p = 0.71$)]. As this single-center study has several limitations including potential biases in selection, sampling, and outcome recall, the results cannot be generalized to all patients with RBD. However, this study demonstrates similar clinical outcomes between melatonin and clonazepam in a moderate-sized patient population in a naturalistic clinical setting [21]. The high representation of patients with neurodegenerative disorders, major depression, and selective serotonin/norepinephrine reuptake inhibitor use seen in this study strengthens the evidence for melatonin in these particular patient populations, which were underrepresented in previous crossover and open-label trials evaluating melatonin in RBD [30–32].

5. Retrospective evidence evaluating melatonin use in RBD

A retrospective case series evaluated the efficacy of initial melatonin monotherapy followed by combination clonazepam therapy in 28 Taiwanese patients with RBD. The majority of patients were referred to the sleep clinic for suspected OSA, followed by insomnia complaints in patients with neurological disease. Patients underwent a systematic interview that included an interview of a bed partner or caregiver. After evaluation of comorbidities and the associated disease states, a PSG evaluation was conducted in addition to electromyogram (EMG) activity scoring. Patients who presented with sleep-disordered breathing were then controlled with nasal continuous positive airway pressure (CPAP). Patients with abnormal EMG activity and sleep behaviors entered into the clinical treatment protocol. A 4-week observational period occurred in which bed partners documented the number of nights with the presence of abnormal sleep behaviors. A second PSG with video monitoring was conducted at the end of the observational period. Patient follow-up involving patient and bed partner interviews and a review of the sleep log of the previous 4 weeks. Additionally, PSG and EMG scorings in REM were conducted the month following the observation period and every other month for a total of 7 months. Of the 28 patients included in the clinical protocol, the mean age was 66.5 years, the mean body mass index was 26.6 kg/m^2, 72% were male, abnormal sleep behavior was reported for 2.5 ± 3.2 years, and movement of extremities while sleeping resulted in mild bed partner trauma in 82% of patients. Comorbid conditions consisted of OSA ($n = 16$), Parkinson's disease ($n = 10$), poor nocturnal sleep ($n = 7$), and cognitive decline ($n = 4$). Although comprehensive medication profiles were not available, medications used for the treatment of neurological disorders were reported as unchanged during the treatment protocol. The two initial patients included in the protocol were started on melatonin 3 mg nightly prior to bedtime; however, no change in reported behavioral patterns or PSG with EMG scoring was found after the first 4 weeks of therapy. These two patients began combination therapy with clonazepam, which was increased from 0.5 to 1 mg nightly after 1 month. After a 2-month follow-up after initiation of clonazepam, the reported behavioral patterns were improved. However, improved behaviors did not persist at the 4-month follow-up, at which melatonin was increased to 6 mg nightly in addition to clonazepam 1 mg nightly. Due to the potentially ineffective 3-mg melatonin dose used in the two initial patients, the clinical protocol was changed to prescribe melatonin 6 mg nightly in the subsequent 26 patient cases reported. These 26 patients underwent 4 months of melatonin therapy, received follow-up, and then were prescribed clonazepam 0.5–1 mg nightly in addition to melatonin until the end of the 7-month clinical protocol. Statistically significant reductions of nights with dream-acting-out and nights with vocalizations from baseline (9.8 ± 5.13 and 9.18 ± 5.13, respectively) were found with melatonin 6 mg nightly at the 4-month follow-up (1.08 ± 2.81 and 0.61 ± 0.96, respectively) and with melatonin 6 mg nightly plus clonazepam 0.5–1 mg nightly at the 6-month follow-up (0.10 ± 0.05 and 0, respectively) ($p \leq 0.001$). Percent WASO was reduced from baseline (11.37 ± 3.25) to month 4 (8.11 ± 2.48) ($p = 0.001$) and further at month 6 (5.53 ± 2.38) (p = n/a). The percentage of high EMG during total REM sleep time was reduced from baseline (46.98 ± 16.66) at month 4 (1.37 ± 2.47) and month 6 (2.55 ± 9.34) ($p = 0.001$). No statistically significant difference was found between the percentage of high EMG during total REM sleep time between months 4 and 6 likely due to small sample size and possible type II error. One patient with idiopathic RBD was followed up past the 7-month follow-up due to treatment failure. This patient was reported to use physical restraints while sleeping in addition to taking 12 mg melatonin and 3 mg clonazepam nightly after 12 months of follow-up. The authors emphasized the importance of affirming an OSA diagnosis and CPAP treatment in patients believed to have RBD. Additionally, the authors state that further research is needed to establish PSG cutoff points in which the elimination of abnormal sleep behaviors will occur as well as further understanding of underlying processes in patients who do not respond to current therapies used in RBD. The limitations to this report are significant for a small sample size, limited duration of follow-up, and no placebo control or randomization. Despite these limitations, important outcomes were found through sleep journaling, structured patient and bed partner interviews, and PSG and EMG evaluations [33].

A second retrospective case series evaluated melatonin in 14 patients with RBD and various comorbid neurologic disorders. The majority of patients were male (93%), had a mean RBD diagnosis at 56 years of age, and had a mean onset of neurologic disorder at

65 years of age. The patients had diagnoses of dementia with Lewy bodies ($n = 7$), mild cognitive impairment with mild parkinsonism ($n = 2$), multiple system atrophy ($n = 2$), narcolepsy ($n = 2$), and Parkinson's disease ($n = 1$). The patients were administered open-label melatonin 3–12 mg (mean 6.75 mg) nightly due to previous incomplete or adverse response to clonazepam, significant dementia, or an OSA diagnosis. The patients were allowed to take psychotropic medications, which included clonazepam ($n = 6$), donepezil ($n = 9$), selective serotonin reuptake inhibitor (SSRI) antidepressants ($n = 5$), carbidopa/levodopa ($n = 4$), and psychostimulants ($n = 2$). PSG recordings were performed in 13 patients, with 12 studies confirming RBD. The duration of patient follow-up was 9–25 months (mean 14 months). Clinical response was reported as controlled in six patients (two patients used concomitant 0.5–1 mg clonazepam), markedly improved in four patients (three patients used concomitant 0.5 mg clonazepam), having short-term benefit in two patients (both taking concomitant 0.5 mg clonazepam), and either no improvement or clinically worsening in two patients. Adverse effects of delusion/hallucination ($n = 1$), headache ($n = 2$), and morning sleepiness ($n = 2$) were reported in patients taking ≥9 mg of melatonin nightly. The authors additionally note that patients taking donepezil showed less significant changes in frequency or severity of RBD symptoms. This single-center, uncontrolled, open-label, primarily male report has several limitations and results cannot be generalized to all patients with RBD. However, this work demonstrates important clinical outcomes in a small population of patients with various neurological diseases and medication profiles [23].

6. Discussion

Treatment with exogenous melatonin for RBD was found to yield a statistically significant decrease in RSWA in one randomized placebo-controlled trial and two open-label trials [30–32]. However, polysomnographic RSWA may be an incidental finding as PSG without clinical symptoms, and RSWA alone cannot be equated with a clinical diagnosis of RBD, so the more important treatment outcomes are behavioral symptom changes in RBD [2]. Kunz and Mahlberg demonstrated that melatonin therapy yielded decreased CGI scores to a greater degree than placebo and reduced symptom severity in a large majority of subjects [30]. Additionally, major reductions from baseline in yelling while sleeping, jumping/falling out of bed, lacerations, fractures, ecchymosis, vigorous sleep behaviors, and frightening dreams were reported, as well as moderate to remarkable clinical improvement in 86% of subjects by Takeuchi and colleagues [32]. Unfortunately, the results of these trials are difficult to generalize among all patients with RBD. Subjects with DSM-IV diagnoses were excluded in two trials and unclear in the third; thus, the results may not be applicable to patients with these diagnoses [30–32]. This is an important consideration as comorbid depression with use of antidepressants could potentially negate any benefit of melatonin. As an example, the frequency of major depression in patients with Parkinson's disease and dementias is estimated to be 17% and 32%, respectively [35,36]. As antidepressants may worsen RBD [37], further investigation is warranted to assess melatonin for the management of RBD in patients with comorbid depression. It may also be difficult to generalize trial results to patients with neurodegenerative disorders as only two subjects were reported to have Parkinson's disease by Kunz and Mahlberg [30] and Kunz and Bes [31], and concomitant diagnoses were not reported by Takeuchi and colleagues [32]. Between approximately 50% and 81% of patients with RBD may develop overt cognitive, motor, or autonomic symptoms of neurodegenerative disease following an initial RBD diagnosis during longitudinal follow-up [2,11,13,14,16,20]. Results from retrospective studies [13,33] shed insight into expected clinical responses in patients with various neurologic disorders and medication regimens seen in clinical practice.

Melatonin is generally well tolerated with minimal adverse events. In a toxicological assessment of 10 mg melatonin nightly for a 28-day period, adverse effects were similar to placebo and included somnolence, headache, fatigue, and cognitive alteration [38]. Additionally, dysgeusia and a decrease of 0.2 °C in body temperature 2–3 h post ingestion have been reported [38,39]. The most common adverse effect associated with melatonin treatment in McCarter et al.'s patient-reported outcome study was sleepiness in 29% of 25 treated RBD patients, followed by trouble thinking (12%), unsteadiness (8%), nausea (8%), dizziness (4%), and sexual dysfunction (8%), and each of these was most frequently rated to be mild in severity [21]. The most commonly used dose in RBD trials was 3 mg nightly before bedtime, with no adverse events reported at this dose [30,31]. Headache and morning sedation were reported in a small number of patients receiving doses of 9 mg or greater, but diminished upon dosage reduction [23]. Given the favorable side-effect profile, melatonin can be an alternative when clonazepam is not tolerated or less ideal for use.

Melatonin's mechanism of action against RBD (see Fig. 1) remains unclear, but it could be mediated by a combination of influences including a direct impact on REM sleep atonia, modulation of gamma-aminobutyric acid (GABA)ergic inhibition, stabilizing circadian clock variability and desynchronization, and increasing sleep efficiency [31,32,34,40,41]. In a glycine/GABA-A receptor knockout transgenic mouse model of RBD, melatonin was more efficacious than clonazepam in decreasing REM motor behaviors and restoring REM muscle atonia [42]. The transgenic mouse model could aid the development and future application of more specific RBD treatments. A neurotransmitter mechanism could also play a role in the pathophysiology of RBD as it has been proposed that the ratio of cholinergic to aminergic activity facilitates REM sleep [43], in which acetylcholine has multiple roles [44]. Though reports of nightmares and enhanced dreaming with acetylcholinesterase inhibitor poisoning are available [45], patients with RBD taking acetylcholinesterase inhibitors have been reported to have both lessened response in RBD outcomes [23] as well as improvement [46]. Melatonin inhibits calmodulin, which then may modulate skeletal muscle acetylcholine receptors [47]. Through this mechanism as well as antioxidant properties, it is believed that melatonin may be important for receptor maintenance in aging persons [48]. It is also presumed that melatonin modulates cytoskeletal structure through its antagonism of calmodulin [49]. As serotonergic medications could be responsible for causing secondary RBD [37], it is important to also consider this mechanism. Serotonin agonism has been shown to induce muscle tonicity in animal gastrointestinal tract [50,51] and human skeletal muscle [52]. The attenuation of serotonin-induced contraction was demonstrated with pretreatment of nifedipine, cromakalim, diazoxide, caffeine, and sodium nitroprusside, but acetylcholine-induced contractions were refractory to these agents, suggesting two distinct contraction pathways [50]. Due to these data, the pathophysiology of RBD could be multifactorial, in which more research is necessary.

Given the proposed novel mechanism of action for melatonin in RBD, it could be likely other melatonin receptor agonists offer utility in RBD. Agomelatine is a melatonin 1 and 2 receptor agonist with 5-hydroxytrypamine 2 agonist activity [53]. In a case series of three patients, agomelatine at doses of 25–50 mg prior to bedtime reduced the frequency and severity of RBD episodes over a period of 6-month follow-up. Reduction of dream production was also noted, which was believed to be due to normalization of REM sleep in addition to enhanced dopamine and noradrenaline activity in the frontal cortex, leading to a subsequent decrease in excitatory glutamate release. Patients tolerated agomelatine and no adverse events were reported [54]. The melatonin receptor agonist ramelteon has

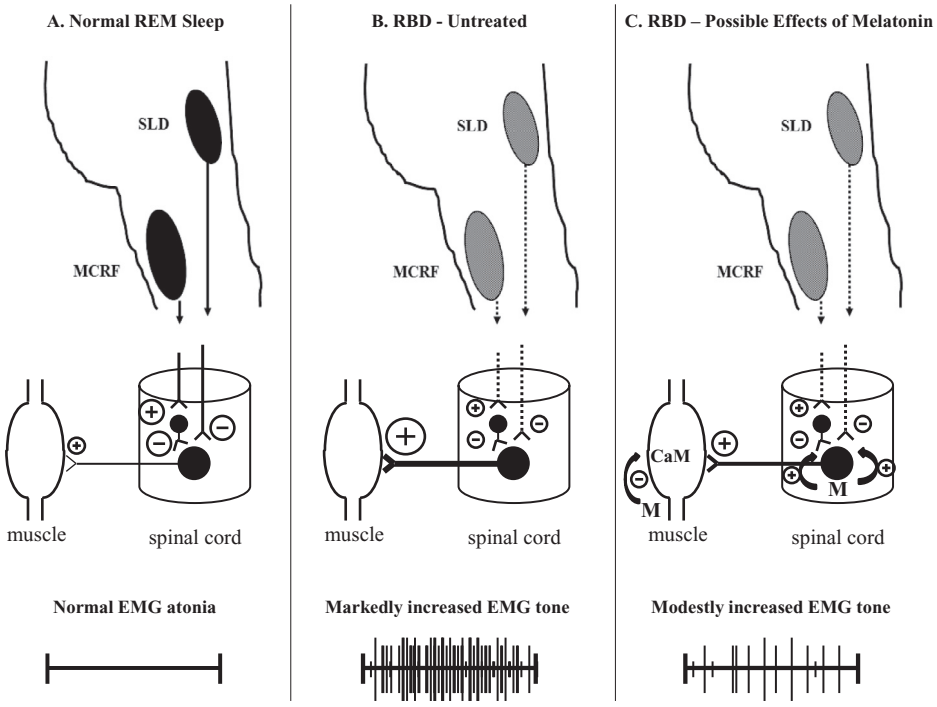

Fig. 1. Speculative Mechanism of Action of Melatonin in RBD. (A) Normal REM sleep physiology. The sublaterodorsal nucleus (SLD) and magnocellular reticular formation (MCRF) nucleus send projections to the anterior horn cell (AHC) neurons in the spinal cord, with the GABAergic ± glycinergic effects on the AHC exerting inhibitory influences (thereby suppressing AHC activity) and resulting in normal EMG atonia. (B) REM sleep behavior disorder. In RBD associated with neurodegenerative disease, the SLD and/or MCRF are presumed to undergo neuronal loss such that their projections on the AHC ultimately have decreased effects. Other projections from brain-stem, diencephalic, and telencephalic structures maintain their excitatory influences on the AHC (for simplicity, these projections are not shown here), resulting in increased EMG tone ± the behavioral aspects of RBD. (C) REM sleep behavior disorder treated with exogenous melatonin. Melatonin may decrease the electrophysiologic and behavioral manifestations of RBD by potentiating the action of GABA on $GABA_A$ receptors on the AHC. Melatonin also may decrease calmodulin, which subsequently may modulate cytoskeletal structure and nicotinic acetylcholine receptor expression in skeletal muscle cells.
The encircled plus symbols represent excitatory influences; the encircled minus symbols represent inhibitory influences, and their relative size represents the degree of the influences. The symbol "M" represents melatonin, with the encircled plus symbols representing the potentiation of GABA on the $GABA_A$ receptors on the AHC. The symbol "CaM" represents calmodulin.

documented evidence in two patients with RBD secondary to multiple system atrophy and Parkinson's disease. Patients took ramelteon 8 mg prior to bedtime and demonstrated clinical RBD improvement as well as decrease in RSWA. Both patients were withdrawn from ramelteon therapy, suffered from enhanced RBD symptoms, and then were continued on the medication for at least two years [55]. As few data are available regarding melatonin receptor agonists in RBD, more research is necessary to determine their potential role in therapy.

Clonazepam is still recommended by many clinicians as the first-line therapy for RBD. The efficacy of this medication has been reported in >300 patients in low-level evidence exclusively retrospective case series reports [20]. In contrast to the seemingly benign adverse-event profile of melatonin, clonazepam is associated with considerable side effects and has the potential for drug interactions. The 2012 Beers Criteria states that benzodiazepines may be appropriate for REM sleep disorders but warns of an increased risk of cognitive impairment, delirium, falls, fracture, and motor vehicle accidents [56]. In a retrospective study of 36 patients being treated with clonazepam for RBD, 58% of patients were noted to have moderate to severe adverse effects, and 36% of patients discontinued therapy due to adverse effects [57]. In McCarter et al.'s report of 18 RBD patients receiving clonazepam, the most common adverse effects were sleepiness (56%), unsteadiness (39%), trouble thinking (39%), dizziness, (22%), sexual dysfunction (17%), and nausea (6%) [21]. In one large review and clinical guide, the most commonly cited adverse effects of clonazepam were sedation, impotence, motor incoordination, and confusion/memory dysfunction [20]. Additionally, clonazepam is a cytochrome P450 substrate, with potentially inducible metabolism by certain antiepileptic drugs such as carbamazepine, which increases the metabolism of clonazepam and reduces its serum concentration, whereas certain other medications such as clarithromycin may instead raise clonazepam serum levels, and increase the risk of toxicity [58]. These risks must especially be considered in RBD treatment given that most RBD patients are elderly and may have motor or cognitive impairments making adverse effects more likely, and many receive polytherapy with other medications [59,60]. Clonazepam is also a potential upper airway suppressant that must be used with caution when treating RBD patients with comorbid OSA. Clonazepam is also rated as pregnancy category D, making it a poor choice for use in women of childbearing potential [61]. Finally, clonazepam is a Food and Drug Administration (FDA) scheduled substance with abuse potential and may not be a treatment of choice in those with either an active or a previous history of substance use disorders [62].

7. Conclusion

Melatonin appears to be an effective medication in RBD [13,21,30–33] and may have a more direct effect on the pathophysiology of RBD than clonazepam [30,31,34]. The pathophysiology of RBD is unknown as is melatonin's mechanism of action. We hypothesize that melatonin's activity as a calmodulin antagonist may impact RBD pathophysiology. Currently, there is no clinical trial that has compared melatonin and clonazepam; however, a consensus statement from the International Rapid Eye Movement Sleep

Behavior Disorder Study Group seeks to devise a high level of evidence study [63]. Until new evidence is made available, the small body of supportive literature and favorable adverse-effect profile make melatonin an attractive treatment option for patients with RBD, especially elderly individuals with underlying neurodegenerative disorders, comorbid sleep apnea, and those receiving polypharmacy with other medications.

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Conflict of interest

BF Boeve reports that he is an investigator in clinical trials sponsored by Cephalon, Inc., Allon Pharmaceuticals, and GE Healthcare. He receives royalties from the publication of a book entitled Behavioral Neurology of Dementia (CambridgeMedicine, 2009). He has received honoraria from the American Academy of Neurology. He serves on the Scientific Advisory Board of the Tau Consortium. He receives research support from the National Institute on Aging (P50 AG016574, U01 AG006786, RO1 AG032306, RO1 AG041797) and the Mangurian Foundation.

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Glossary

Atonia lack of tone or energy
Phasic muscle twitches percentage of 20-s mini-epochs of REM with at least one muscle twitch
REM density percentage of 3-s mini-epochs of REM with at least one REM
REM onset latency interval between lights off and first epoch of sleep other than stage REM
Sleep efficiency percentage of total sleep time on sleep period time
Sleep onset latency interval between lights off and first epoch of sleep other than stage NREM
Sleep period time interval between first and last epoch stage in NREM 2, 3, and 4 or REM
Total sleep time sum of all epochs in NREM 1, 2, 3, and 4, and REM
Wake after sleep onset time spent awake after sleep initiation before final awakening